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Central Venous Catheter Thrombosis among Pediatric Patients Admitted to the Intensive Care Unit

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ABSTRACT

Objective: To identify the incidence and risk factors for Central Venous Catheter-Related Thrombosis (CVC-RT) among patients admitted to the pediatric intensive unit.

Design: Prospective observational study

Setting: King Abdulaziz Medical City, a tertiary care center in the western region of Saudi Arabia.

Patients: Pediatric patients aged one to 168 months who were admitted to the PICU and required central line insertion (whether inserted centrally or peripherally) more than 48 hours were included. Screening for thrombosis was done within day 4-7 post line insertion and again on day 14.

Interventions: None

Measurements and main results: A total of 255 patients were enrolled over a period of 17 months. The incidence rate of CVC-RT was 5.4%. The type of CVC was significantly different between the two groups; in the no thrombosis group, 59.2% had central-line while in the CVC-RT groups and 51.9% had PIC line (p=0.027). In a multivariate regression analysis including patients' clinical profile, high d-dimer as baseline and low platelets were both significant risk factors for CVC-RT (adjusted OR=3.22, CI (1.25-8.28), p=0.015 and adjusted OR=7.38, CI (2.18-25.02), p=0.001), respectively.

Conclusions: The current study found out that PIC-line was associated with increased risk of CVC-RT, which is congruent with the literature. As children with CVC can have multiple risk factors to develop

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CVC-RT, it is important to conduct further large prospective studies to identify such factors and decrease the incidence of CVC-RT.

Keywords: Central venous catheter-related thrombosis; Pediatric intensive unit; Intensive care unit; Screening

INTRODUCTION

Central Venous Catheter (CVC) is a necessary and important tool in the management of acutely ill children and those in need of complex care. It provides an access to infuse venous medication, fluids, blood products, chemotherapy, total parental nutrition as well as painless withdrawal of blood for laboratory testing when needed [1].

CVC-Related Thrombosis (CVC-RT) remains a constant peril among patients admitted to the Pediatric Intensive Care Unit (PICU). Such patients possess two important extrinsic risk factors for thrombosis; line insertion by itself and the admission to the PICU [2]. The exact incidence of CVC-RT is still unclear. It is variable depending on setting, patient age, presence of risk factors and/or symptoms, type and location of line, duration of line *in-situ* and patient flow. The incidence of asymptomatic CVC-RT in a recent study has been estimated to be 22% [3]. The rate of symptomatic CVC-RT has been estimated to be 9.9% as superficial and 18.2% as deep thrombosis [4].

It is not surprising; therefore, that CVC-RT has been a focus of research. Many researches were conducted to identify ways for early detection of CVC-RT before symptoms and signs of thrombosis to intervene and decrease the risk of its complication. The use of anti-coagulants was entertained as prophylaxis for CVC-RT in many different clinical settings [5]. However, recent systemic reviews and meta-analyses also showed no evidence that thromboprophylaxis have decreased the risk of CVC-RT in children [6].

The focus also has been directed toward screening for asymptomatic CVC-RT and whether this cohort should be treated with anticoagulants. One recent study has focused on asymptomatic CVC-RT with 2 years' follow-up and concluded that acute and long-term complication are low and challenged the use of anticoagulant therapy in such cases. The use of routine screening for CVC-RT among asymptomatic patients have not been encouraged in a previous study given that the clinically significant was unclear and the possibility for it to be time and resource consuming.

This article reports the outcomes of a prospective study that aimed to identify the incidence and risk factors for CVC-RT among patients admitted to the PICU in a tertiary care center in the western region of Saudi Arabia. The study also looked into whether bedside Ultrasound (US) screening for CVC-RT within a week of insertion would early detect asymptomatic CVC-RT.

MATERIALS AND METHODS

This was a prospective, observational, single centre study that was conducted over a period of 17 months from September 2019 to January 2021 at King Abdulaziz Medical City, Jeddah, Saudi Arabia. It included patients from the Pediatric Intensive Care Unit (PICU), admitted from pediatric general, haematology/oncology and surgery wards, paediatric cardiac intensive care unit and paediatric burn unit. Total number of admissions in the above-mentioned units and wards is around 1000 admissions per year. Total number of central-line insertion in paediatric population in our centre is around 150-300 cases per year.

Inclusion Criteria

All pediatric patients aged one to 168 months admitted to out Centre and required central line insertion (whether inserted centrally or peripherally) within the study period. The line must have been inserted for more than 48 hours and centrally inserted lines must be guided by ultrasound, which was the routine practice in our Centre. The decision regarding what type of central venous catheter the patient would have been based on the expertise of the available PICU staff and patient's clinical condition. The tip of the central line should be placed within the superior vena cava.

Exclusion Criteria

We excluded patients with umbilical central line.

Data Collection

Electronic medical records of the enrolled patients were used to collect multiple variables including demographics, type and brand of line, site of insertion, number of attempts for insertion, number of lumens, weather patient has a high risk for thrombosis or not; we identified high risk factors for thrombosis as having sickle cell anemia, any thrombophilia, congenital cyanotic heart disease, sepsis or previous thrombosis.

Screening for thrombosis was done within day 4-7 post line insertion and again on day 14; an add-on screening also took place if clinically indicated. Screening was done by trained PICU staff who received US training courses or by a medical radiologist. US probe was used to gently compress veins of interest. Inability to compress the vein or partially occluded veins is considered positive for CVC-RT screening. All patients with positive screening underwent official US as the diagnosis of CVC-RT was only done by an official US, performed and interpreted by a medical radiologist; clinical suspicion alone was not considered enough evidence of making the diagnosis

of CVC-RT. Routine heparinization of central line was not a routine practice in our centre unless for Hep-lock when the line was not in use.

Coagulation laboratory markers (D-dimer, fibrinogen and platelet count) were measured for all patients before line insertion. Abnormal d-dimmer, fibrinogen and platelets were defined as values >0.5 mg/L, >4 g/L and <150 × 10^9/L, respectively.

Outcome and Assumptions

We hypothesized that peripherally inserted central catheters would be associated with an increased risk of deep vein thrombosis and that this association would persist after the adjustment of clinically important covariates

Statistical Analysis

Continuous variables with normal distributions were described as mean and Standard Deviation (± SD); median and interquartile ranges were used for data with skewed distribution. The outcome for bivariate analysis was the development of CVC-RT. Student-t test and Mann-Whitney U tests were used when comparing contentious data. Categorical measures were compared by Pearson *Chi-square* test or Fisher exact test. P-value of less than 0.05 was defined as statistically significant. All statistical analyses have been performed using Statistical Package for the Social Sciences (SPSS) version 26.00.

RESULTS

A total of 255 patients were enrolled. The overall median age was 48 months with the majority of patient were males (53%). Oncology patients accounted for 51% (130/255) of the enrolled patients. Screening on day 5 post-insertion for CVC-RT took place for 92% of the patients and on day 14 for 42%. The incidence rate of CVC-RT over the 17 months study period was 5.4%.

The demographics and clinical characteristics between patients who developed CVC-RT and those who did not. The median age in both groups was 48 months and there was no significant difference in terms of male sex between patients who developed CVC-RT and those who did not (51.9% *vs.* 53.5% respectively, p=0.8710). Clinical factors were significantly more evident among patients who developed CVC-RT (55.6% *vs* 6.6%, p<0.001). 14.8% of patient with CVC-RT had high risk factor compared to 25.4% in the no CVC-RT group (p=0.224).

Table 1 shows the difference of CVC profile and laboratory markers between patients who developed CVC-RT and those who did not. Most CVC in both groups were inserted electively (>85%). The type of CVC was significantly different between the two groups; in the no thrombosis group, 59.2% had central-line while in the CVC-RT groups, 51.9% had PIC line (p=0.027). There was no significant difference regarding overall number of lumens, irrespective of CVC type, between patients who developed CVC-RT and those who did not (p=0.107). **Supplementary File** illustrates a comparison between the two patient groups regarding the types of CVC with the number of lumens (line/lumen).

Table 1: The difference of Central Venous Catheter (CVC) profile and laboratory markers between patients who developed CVC- Related Thrombosis (CVC-RT) and those who did not

Variables	Total patients with central line=255		p-value
	No CVC-RT	CVC-RT	
	n=228 (%)	n=27 (%)	
	Indication		
Elective	197 (86.4)	26 (96.3)	0.142
Emergency	31 (13.6)	1 (3.7)	
	Type of CVC		
Central-line	135 (59.2)	8 (29.6)	0.011
Implantable lines*	30 (13.2)	5 (18.5)	
PIC-line	63 (27.6)	14 (51.9)	
	Overall number of line lumens		
One	40 (17.5)	3 (11.1)	0.107
Two	87 (38.2)	16 (59.3)	
Three	101 (44.3)	8 (29.6)	

	Number of attempts (%)		
One time	42 (18.4)	1 (0.4)	0.117**
Two times	134 (58.8)	17 (63)	
>Two times	52 (22.8)	9 (33.3)	
Median duration with a line in days (IQR)	22 (15)	30 (12)	0.087
Median duration till thrombosis occurs in days (IQR)	22 (15)	30 (12)	Not Applicable***

Note: PIC line: Peripherally inserted central-line; IQR: Interquartile range. *Chi-square*. * Porta cath/Hickman/Proveac. **1 cell (16.7%) has expected count less than 5. The minimum expected count is 4.55. *** There were many outliers in the thrombosis group.

Screening for CVC-RT on day 4-7 of insertion by bed-side US was done for 82.1% of patients. 11 patients had positive screening for CVC-RT; however, only 2 patients (19% out of 11) had con irmed diagnosis of CVC-RT. On day 14, only 41.2% of patient had screening. Only on patient had his screening positive and his official US came back positive too. **Table 2** shows details regarding the screening for CVC-RT. The reasons for low screening among the sample was the transfer of the patient to other units, discharge from the hospital or applicability as the diagnosis of CVC-RT was made before the screening.

Table 2: Central Venous Catheter-Related Thrombosis (CVC-RT) screening details.

Variables	Total patients with CVC=255	
	Screening status	Positive official US
	Day 4-7 screening	
Negative	197 (77.3)	Not required
Positive	11 (4.8)	2 (19% out of 11)
Not done/not applicable	20 (4.3)	-
	Day 14 screening	
Negative	104 (40.8)	Not required
Positive	1 (0.39)	1 (100% out of 1)
Not done/Not applicable	123 (48.2)	-

Table 3 shows univariate analysis for possible independent variables that might affect the development of CVC-RT. For example, female sex, age ≥ 6 years and having a high risk were not found to be significant predictors for CVC-RT (p=0.870, 0.666 and 0.224 respectively). Patients who developed CVC-RT had significantly low platelets (OR=2.49, (1.01-6.15), p=0.043) and high d-dimer as baseline (OR=5.53, (1.70-17.96), p=0.002). Patients with central line were found to have less CVC-RT compared to others (OR=0.29 (0.12-0.69), p=0.008).

Table 3: Univariate regression analysis of independent variables affecting/predicting the development of Central Venous Catheter-Related Thrombosis (CVC-RT)

Variables	Developed CVC-RT n=27 (%)	Odds ratio (CI)	p-value
Sex (female)	13 (48.1)	1.07 (0.48-2.38)	0.87
Age ≤ 1 year	5 (18.5)	0.98 (0.35-2.73)	0.966
Age ≤ 2 year	7 (25.9)	0.74 (0.30-1.84)	0.519
Age ≥ 6 years	10 (37)	1.20 (0.52-2.75)	0.666

Sepsis as primary diagnosis	9 (33.3)	1.08 (0.46-2.53)	0.853
Oncological as primary diagnosis	14 (51.9)	1.04 (0.47-2.31)	0.924
High risk	4 (14.8)	0.51 (0.17-1.54)	0.224
Low platelets as baseline	8 (29.6)	2.49 (1.01-6.15)	0.043
High d-dimer as baseline	5 (18.5)	5.53 (1.70-17.96)	0.002
High fibrinogen as baseline	1 (3.7)	2.5 (0.23-20.0)	0.49
Central-line	8 (29.6)	0.29 (0.12-0.69)	0.003
PIC-line	14 (51.9)	2.82 (1.26-6.33)	0.014
Implantable line	5 (18.5)	1.50 (0.53-4.26)	0.444
1-lumen line	3 (11.1)	0.59 (0.17-2.05)	0.399
2 or 3-lumens line	24 (88.9)	1.70 (0.49-5.93)	0.399

Multivariate regression analysis for line pro ile was not performed in this study as 81.3% of patient's 2-lumen line who developed CVC-RT with had PIC-line. In a multivariate regression analysis including patients' clinical pro ile (**Table 4**), high d-dimer as baseline and low platelets were both signi icant risk factors for CVC-RT (adjusted OR=3.22, CI (1.25-8.28), p=0.015 and adjusted OR=7.38, CI (2.18-25.02), p=0.001), respectively.

Table 4: Multivariate analyses for risk factors/predictors associated with central-line related thrombosis (CVC-RT)

Variables	Total patients with central line = 255		Crude Odds Ratio* (CI)	p-value	Adjusted odds ratio* (CI)	p-value
	No CVC-RT n=29	Developed CVC-RT n=25				
Clinical profile model						
Low platelets as baseline	33 (14.5)	8 (29.6)	2.49 (1.00-6.15)	0.043	3.22 (1.25-8.28)	0.015
High d-dimer as baseline	9 (3.9)	5 (18.5)	5.53 (1.70-17.96)	0.002	7.38 (2.18-25.02)	0.001

DISCUSSION

Over 17 months, the incidence of CVC-RT was 5.4% in our PICU. Screening for CVC-RT was done in >90% of the enrolled patients on day 4-7. No significant difference was found between patient who developed CVC-RT and those who did not in terms of demographic data. Patients with high d-dimer and low platelets before line insertion were more likely to have CVC-RT.

The incidence of CVC-RT varied in the literature depending on the setting, type of line and the clinical and demographic profiles of patients. The incidence of CVC-RT in the PICU was estimated by 3% by a large study conducted in the US [7]. Locally, only one study estimated an overall incidence of CVC-RT to be 8.6% and it was only among patients with central-line [8]. The incidence of CVC-RT in the PICU in the current study is similar to those reported the literature.

In a study conducted among patients with central-line, male sex was deemed a significant predictor for CVC-RT (OR=1.38, CI (1.00-1, 90), p=0.049 [9]. Such finding was also endorsed by a recent study [10]. In a previous study, however, the effect of sex among patients with PIC-line who developed CVC-RT was investigated and no significant effect was found [11]. CVC-RT was also found to be among infants compared to other age groups [12]. The current study showed no difference in regard to demographic data between all patients who developed CVC-RT and those who did not.

CVC type and the risk for thrombosis has remained a critical question with varied study results in the literature. It is still unsettled what type of line is superior when it comes to the risk of developing CVL thrombosis [13]. It has been theoretically believed, however, that PIC-line pose a higher risk to develop CVC-RT as it occupies a large portion of the vessel's lumen compared to tunneled lines [14]. In comparison to central-line, PIC-line was found to be

significantly associated with CVC-RT (OR=2.71; 95% CI (1.65-4.45), p<0.0001) [15]. In a recent study compared PIC-line to tunneled (implantable) lines, PICC-line posed significantly higher Hazard Ratio (HR) for CVC-RT (HR=8.5, CI (3.1-23), p<0.001). Regardless, the use of PIC-line significantly increases as the placement and removal can be done bedside with little to no sedation [16]. However, in another study that also compared PIC-line and implantable lines, no significant difference in incidence was found comparing the two groups (p=0.38) [17]. In the current study and in comparison to all central venous catheters, CVC-RT was significantly more among patients with PIC-line.

Multiple lumen central line was associated with increased occurrence of CVC-RT mainly due to the larger size of the catheter compared to single lumen [18]. In a recent study by Jaffray, et al, multi-lumen CVC among patients with PIC-line and tunneled line has a hazard of 3.9 for CVC-RT (95% CI (1.8-8.9); p=0.003). Other studies, however, found that "double-lumen" lines were safer compared to single lumen. In the current study, ≥ 2 lumen line has not been identified to be a significant risk factor for CVC-RT. This can be explained by the fact that the majority of the enrolled patient had PIC-line.

The most common site for central line site is the femoral vein [18]. However, the recommended site for central line insertion as per international guidelines and many studies is the jugular vein [19-21]. Femoral and sub-Clavian veins are reported to have higher incidence of CVC-RT. Femoral CVC has been associated with higher rates of acute complications and residual thrombosis at even 2 years follow up. Such comparisons were not done in the current study as the location of the lines was varied for patients with central line.

There are other risk factors associated with increased risk of CVC-RT such as having cancer, Congenital Heart Disease (CHD), sickle cell disease, trauma, metabolic disorders, renal diseases, cystic fibrosis and being dependent on Total Parental Nutrition (TPN). Such risk factors could not be identified in the current study, which could be attributed to the less varied patient-flow to the unit.

D-dimer is known and has been reported in many studies to be increased among patients with CVC-RT and could also facilitate timely detection. In a study conducted by Li et al., D-dimer increased significantly among patients with CVC-RT (3.4 ± 4.9 *vs.* 2.2 ± 3.8, p<0.001). In a study conducted among adults, it was found that high d-dimer level was significantly associated with the occurrence of future venous thrombosis. In the current study, high D-dimer before inserting a CVC was associated with increased risk of CVC-RT. However, due to the variability of td-dimer level no specific cutoff could be identified.

Platelet count was also investigated and proposed to increase the risk of CVC-RT. Li, et al., found out the platelet count has a high-impact factor but with overlapping in a fusion model to identify risk factors for CVC-RT. In the current study, patients with low platelets before line insertion were significantly at higher risk to develop CVC-RT.

The current study has several limitations. It included only one tertiary center in Saudi Arabia. The effect of weight and catheter-to-vein ratio was no studied. Not all the previous studied risk factors for CVC-RT could be studies given the variability of patient flow in our center.

CONCLUSION

CVC-RT remains a focus of research in the PICU. The current study found out that PIC-line was associated with increased risk of CVC-RT, which is congruent with the literature. Children with CVC can have multiple risk factors to develop CVC-RT, which highlights the important for further large prospective studies to identify such factors and decrease the incidence of CVC-RT.

ETHICAL CONSIDERATIONS

Informed consent was obtained from all caregivers to participate in the study. The study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical City Research Centre (KAIMRC) under the protocol RJ19/036/J.

DECLARATION OF CONFLICTING INTERESTS

The authors declare no conflict of interest in regard to the research, authorship and/or the publication of this article.

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ETHICAL APPROVAL

This study was approved by the Institutional Review Board (protocol number RJ19/036/J).

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